(HAPOP), the polynucleotides encoding HAPOP, and variants thereof, and the use of these compositions for the diagnosis of inherited and acquired genetic disorders, expression profiling, toxicology testing, and drug development with respect to diseases and disorders associated with apoptosis.

Nucleic acids encoding HAPOP-1 (SEQ ID NO:1), HAPOP-2 (SEQ ID NO:3), HAPOP-3 (SEQ ID NO:5), and HAPOP-4 (SEQ ID NO:7) of the invention were first identified in Incyte Clones 157658 from the promonocyte cDNA library (THP1PLB02), 642272 from the breast cDNA library (BRSTNOT03), 1453807 from the penis tumor cDNA library (PENITUT01), and 2059022 from the ovarian cDNA library (OVARNOT03), respectively, using a computer search for amino acid sequence alignments. Consensus sequences, SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, and SEQ ID NO:8, respectively, were derived from overlapping and/or extended nucleic acid sequences.

HAPOP-1 is 480 amino acids in length and has one potential N-glycosylation site at N262; eight potential casein kinase II phosphorylation sites at S51, S130, S193, S227, S238, S371, S411, and S458; and five potential protein kinase C phosphorylation sites at S181, S193, S428, S458, and T470. Both BLOCKS and PRINTS analyses indicate that regions of HAPOP-1 show similarity to conserved motifs in ICE. These regions extend from P250 to R303, from F308 to G316, and from S344 to S363. A region of unique sequence in HAPOP-1 from about amino acid 203 to about amino acid 212 is encoded by a fragment of SEQ ID NO:2 from about nucleotide 1218 to about nucleotide 1247. Northern analysis shows the expression of this sequence in various libraries, at least 61% of which are associated with proliferating or cancerous tissue and at least 35% of which are associated with the immune response. In particular, 26% of the libraries expressing HAPOP-1 are derived from reproductive tissue.

HAPOP-2 is 238 amino acids in length and has four potential casein kinase II phosphorylation sites at S48, S62, T90, and T164 and four potential protein kinase C phosphorylation sites at S21, S36, S53, and S131. As shown in Figures 1A and 1B, HAPOP-2 has chemical and structural similarity with mouse FSP-27 (SWISS-PROT P56198; SEQ ID NO:9) and human DFF-45 (GI 2065561; SEQ ID NO:10). In particular, HAPOP-2 and FSP-27 share 79% identity, and HAPOP-2 and DFF-45 share 18% identity. In addition, the potential phosphorylation sites at S48, S62, T164, and S131 in HAPOP-2 are conserved in FSP-27, and the potential phosphorylation site at T90 in HAPOP-2 is conserved in both FSP-27 and DFF-45. Like FSP-27, HAPOP-2 is a basic protein with a predicted isoelectric point of 8.8. A region of unique sequence in HAPOP-2 from about amino acid 31 to about amino acid 40 is encoded by a fragment of SEQ ID NO:4 from about nucleotide 229 to about nucleotide 258. Northern analysis shows the expression of this sequence in various libraries, at least 55% of which are associated with proliferating or cancerous tissue and at least 48% of which are associated with the immune response. In

particular, 35% of the libraries expressing HAPOP-2 are derived from reproductive tissue, and 30% are derived from gastrointestinal tissue.

HAPOP-3 is 410 amino acids in length and has one potential N-glycosylation site at N237; one potential cAMP- and cGMP-dependent protein kinase phosphorylation site at S182; eight potential casein kinase II phosphorylation sites at S28, S182, S209, S239, S243, S247, S314, and S323; eight potential protein kinase C phosphorylation sites at S14, S28, T100, T157, T264, S301, S382, and T396; and two potential tyrosine kinase phosphorylation sites at Y137 and Y188. As shown in Figures 2A and 2B, HAPOP-3 has chemical and structural similarity with mouse Req (GI 606661; SEQ ID NO:11). HAPOP-3 and Req share 20% identity. In particular, the region of HAPOP-3 from I291 to Q391 is 44% identical to the corresponding region of Req, which comprises the cluster of four unique zinc finger motifs. All 16 cysteine and histidine residues required for metal binding in Req are conserved in HAPOP-3. A region of unique sequence in HAPOP-3 from about amino acid 36 to about amino acid 45 is encoded by a fragment of SEQ ID NO:6 from about nucleotide 181 to about nucleotide 210. Northern analysis shows the expression of this sequence in various libraries, at least 67% are associated with proliferating or cancerous tissue and at least 33% are associated with the immune response. In particular, 35% of the libraries expressing HAPOP-3 are derived from reproductive tissue, and 27% are derived from gastrointestinal tissue.

HAPOP-4 (SEQ ID NO:12) is 211 amino acids in length and has two potential N-glycosylation sites at N189 and N205; one potential casein kinase II phosphorylation site at S206; two potential protein kinase C phosphorylation sites at S63 and S206; and a potential signal peptide sequence from M1 to about C24. As shown in Figure 3, HAPOP-4 has chemical and structural similarity with hRVP1 (GI 2570129; SEQ ID NO:12). In particular, HAPOP-4 and hRVP1 share 44% identity. Hydrophobicity plots demonstrate that the four transmembrane domains of hRVP1 are well conserved in HAPOP-4 from about amino acid 1 to about amino acid 29; from about amino acid 78 to about amino acid 103; from about amino acid 120 to about amino acid 140; and from amino acid 162 to about amino acid 186. A region of unique sequence in HAPOP-4 from about amino acid 30 to about amino acid 39 is encoded by a fragment of SEQ ID NO:8 from about nucleotide 520 to about nucleotide 549. Northern analysis shows the expression of this sequence in various libraries, at least 70% are associated with proliferating or cancerous tissue and at least 30% are associated with the immune response. In particular, 38% of the libraries expressing HAPOP-4 are derived from reproductive tissue, and 24% are derived from gastrointestinal tissue.

The invention also encompasses HAPOP variants. The claimed HAPOP variants have at least

90% amino acid sequence identity to the HAPOP amino acid sequence.

The invention also encompasses polynucleotides which encode HAPOP (i.e., SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, and SEQ ID NO:8) and variant polynucleotide sequences encoding HAPOP. In particular, such a variant polynucleotide sequence have at least 90% polynucleotide sequence identity to the polynucleotide sequence encoding HAPOP. The polypeptides and polynucleotides of the instant invention are described through the specification.

## Amendments

The above amendments of claims 21 and 27-28 (as well as non-elected claims 31, 34, and 37) place the application in better condition for allowance. Specifically, these amendments obviate Examiner's rejection listed in paragraphs 9b-9c 12b, and 16-19 of the Office Action to which this communication is responsive.

Claims 29-30 along with newly added claims 41-42 are methods of use of the polypeptides of claim 21 which should be examined together, per the Commissioner's Notice in the Official Gazette of March 26, 1996, entitled "Guidance on Treatment of Product and Process Claims in light of *In re Ochiai, In re Brouwer* and 35 U.S.C. § 103(b)" which sets forth the rules, upon allowance of product claims, for rejoinder of process claims covering the same scope of products.

No new matter has been added by these amendments.

## Priority claims under 37 CFR § 1.78

Examiner states that the instant application, filed under former 37 CFR § 1.62, lacks the necessary claim to priority of the parent application (U.S. Patent No.: 09/078,402; Incyte Docket No.: PF-0519 US). Applicants note that the instant divisional application was filed under 37 CFR § 1.53(b) and an amendment inserting a statement of priority to the parent application was included at the time of filing. Applicants request entry of this amendment into the instant application if it has not yet been entered. For the Examiner's convenience, the amended is reiterated, below:

**Please insert the following sentence immediately after the title and before the first sentence of the above identified application:**

– This application is a divisional application of U.S. application Serial Number 09/078,402, filed May 13, 1998. --

## Drawings

The Draftsperson objected to Applicants' drawings under 37 CFR § 1.84(g). Applicants submit

herewith amended drawings.

**Rejections under 35 U.S.C. §§ 101 and 112, first and second paragraphs**

Claims 21-22 and 27-28 stand rejected under 35 U.S.C. § 112, first paragraph, as:

"...containing subject matter which was not described in the specification in such a way as to convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention." [page 5 of Office Action]

Specifically, paragraph 9 of the Office Action alleges that:

9a. "The specification while being enabling for the polypeptides having the sequence of SEQ ID NO:3 or SEQ ID NO:5, does not reasonably provide enablement for variants that have at least 90% sequence identity." "Likewise, it would seem that specific function(s) would be required to make a protein useful for the applications disclosed in the specification. The specification does not teach what those are or how to determine what they are." [page 5]

9b. "The specification while being enabling for a composition comprising a polypeptide of claim 21 and a pharmaceutically acceptable carrier, does not reasonably provide enablement for a "pharmaceutical composition comprising these same components." [page 6]

9c. "Claim 27 is drawn broadly to "...an effective amount...". The claimed invention is not described in such, full clear and concise exact term to enable any person skilled in the art to make and use the same." [page 7]

Claims 21 and 22 are also rejected under 35 U.S.C. § 112, first paragraph, as being "...drawn to a large genus of molecules...encompass[ing] a variety of subgenera with widely varying attributes." [paragraph 10; page 7]

Claims 21, 22, 27, and 28 are also rejected under 35 U.S.C. § 112, second paragraph as being indefinite as a result of the use of the terms "naturally-occurring" and "effective amount". [paragraphs 12a and 12b, respectively; page 9].

**Rejections under 35 U.S.C. § 101**

Claims 21-22 and 27-28 stand rejected under 35 U.S.C. § 101 "because the claimed invention is not supported by either a specific or substantial asserted utility or a well established utility." [paragraph 14; page 9].

**Applicants Resp nse to Rejections under 35 U.S.C. §§ 101 and 112, first paragraph**

The amendments submitted herein obviate objections 9b and 9c, and 12b, above. With respect to

the remaining objections (paragraphs 9a, 10, 12a, and 14), Applicants submit that these rejections are improper, as detailed below:

**The rejection of claims 21, 22, 27, and 28 is improper, as the claims have a patentable utility as set forth in the instant specification, and/or a utility well-known to one of ordinary skill in the art.**

The invention at issue is a **polypeptide** sequence corresponding to a **gene** that is expressed in human reproductive, neurological, and immunological tissues. As such, the claimed invention has numerous practical, beneficial uses in toxicology testing, drug development, and the diagnosis of disease, none of which necessarily require detailed knowledge of how the polypeptide coded for by the polynucleotide works. As a result of the benefits of these uses, the claimed invention already enjoys significant commercial success.

Any of these uses meets the utility requirements of 35 U.S.C. § 101 and, derivatively, § 112, first paragraph. Under these sections of the Patent Act, the patent applicant need only show that the claimed invention is "practically useful," *Anderson v. Natta*, 480 F.2d 1392, 1397, 178 USPQ 458 (CCPA 1973) and confers a "specific benefit" on the public. *Brenner v. Manson*, 383 U.S. 519, 534-35, 148 USPQ 689 (1966). As discussed in a recent Court of Appeals for the Federal Circuit case, this threshold is not high:

> An invention is "useful" under section 101 if it is capable of providing some identifiable benefit. See *Brenner v. Manson*, 383 U.S. 519, 534 [148 USPQ 689] (1966); *Brooktree Corp. v. Advanced Micro Devices, Inc.*, 977 F.2d 1555, 1571 [24 USPQ2d 1401] (Fed. Cir. 1992) ("to violate Section 101 the claimed device must be totally incapable of achieving a useful result"); *Fuller v. Berger*, 120 F. 274, 275 (7th Cir. 1903) (test for utility is whether invention "is incapable of serving any beneficial end").

*Juicy Whip Inc. v. Orange Bang Inc.*, 51 USPQ2d 1700 (Fed. Cir. 1999). In *Stiftung v. Renishaw PLC*, 945 F.2d 1173, 1180, 20 USPQ2d 1094 (Fed. Cir. 1991) the United States Court of Appeal for the Federal Circuit explained:

> An invention need not be the best or only way to accomplish a certain result, and it need only be useful to some extent and in certain applications: "[T]he fact that an invention has only limited utility and is only operable in certain applications is not grounds for finding lack of utility." *Envirotech Corp. v. Al George, Inc.*, 730 F.2d 753, 762, 221 USPQ 473, 480 (Fed. Cir. 1984).

If persons of ordinary skill in the art would understand that there is a "well-established" utility for the claimed invention, the threshold is met automatically and the applicant need not make any showing to demonstrate utility. Manual of Patent Examination Procedure at § 706.03(a). Only if there is no "well-established" utility for the claimed invention must the applicant demonstrate the practical benefits of the invention. *Id.*

Once the patent applicant identifies a specific utility, the claimed invention is presumed to possess it. *In re Cortright*, 165 F.3d 1353, 1357, 49 USPQ2d 1464; *In re Brana*, 51 F.3d 1560, 1566; 34 USPQ2d 1436 (Fed. Cir. 1995). In that case the Patent Office bears the burden to demonstrate that a person of ordinary skill in the art would reasonably doubt that the asserted utility could be achieved by the claimed invention. *Ids.* To do so, the PTO must provide evidence or sound scientific reasoning. *See In re Langer*, 503 F.2d 1380, 1391-92, 183 USPQ 288 (CCPA 1974). If and only if the Patent Office makes such a showing, the burden shifts to the applicant to provide rebuttal evidence that would convince the person of ordinary skill that there is sufficient proof of utility. *Brana*, 51 F.3d at 1566. The applicant need only prove a "substantial likelihood" of utility; certainty is not required. *Brenner*, 383 U.S. at 532.

The rejection fails to demonstrate either that the Applicants' assertions of utility are legally insufficient or that a person of ordinary skill in the art would reasonably doubt that they could be achieved. For these reasons alone the rejections should be overturned.

There is, however, an additional, independent reason to overturn the rejections: to the extent the rejections are based on Revised Interim Utility Examination Guidelines (64 FR 71427, December 21, 1999) and Revised Interim Utility Guidelines Training Materials (USPTO Website www.uspto.gov, March 1, 2000), the Guidelines and Training Materials are themselves inconsistent with the law. These inconsistencies are discussed separately below.

## I. The use of toxicology testing, drug development, and the diagnosis of disease, none of which necessarily require detailed knowledge of how the polypeptide are sufficient utilities under 35 U.S.C. §§ 101 and 112, first paragraph

The claimed invention meets all of the necessary requirements for establishing a credible utility under the Patent Law: There is a "well-established" use for the claimed invention, there are specific practical and beneficial uses for the invention, and those uses are substantial. Objective evidence, not considered by the Patent Office, further corroborates the credibility of the asserted utilities.

### A. The use of human polynucleotides and their encoded polypeptides as tools for toxicology testing, drug discovery, and the diagnosis of disease is "well-established"

In recent years, scientists have developed important techniques for toxicology testing, drug development, and disease diagnosis. Many of these techniques rely on expression profiling, in which the expression of numerous genes is compared in two or more samples. Genes or gene fragments known to be expressed, such as the invention at issue, are tools essential to any technology that uses expression profiling. Knowledge of the function of the polypeptide that a polynucleotide encodes is not necessary

for the use of the polynucleotide in expression profiling. The fact that the expression profile of a naturally occurring polynucleotide is altered in a sample treated with a test compound is highly relevant in toxicology testing even in the absence of a known function for the encoded polypeptide.

Likewise, proteome expression profiling techniques have been developed in which the expression of numerous polypeptides is compared in two or more samples. Polypeptide or polypeptide fragments known to be expressed are tools essential to any technology that uses proteome expression profiling. See, *e.g.,* Sandra Steiner and N. Leigh Anderson, Expression profiling in toxicology -- potentials and limitations, Toxicology Letters 112-13:467 (2000).

The technologies made possible by expression profiling and the DNA and polypeptide tools upon which they rely are now well-established. The technical literature recognizes not only the prevalence of these technologies, but also their unprecedented advantages in drug development, testing and safety assessment. One of these techniques is toxicology testing, used in both drug development and safety assessment. Toxicology testing is now standard practice in the pharmaceutical industry. See, *e.g.*, John C. Rockett, et al., Differential gene expression in drug metabolism and toxicology: practicalities, problems, and potential, Xenobiotica 29(7):655, 656 (1999):

> Knowledge of toxin-dependent regulation in target tissues is not solely an academic pursuit as much interest has been generated in the pharmaceutical industry to harness this technology in the early identification of toxic drug candidates, thereby shortening the developmental process and contributing substantially to the safety assessment of new drugs.

To the same effect are several other scientific publications, including Emile F. Nuwaysir, et al., Microarrays and Toxicology: The Advent of Toxicogenomics, Molecular Genesis 24:153 (1999); Sandra Steiner and N. Leigh Anderson, *supra.*

Nucleic acids useful for measuring the expression of whole classes of genes are routinely incorporated for use in toxicology testing. Nuwaysir et al. describes, for example, a Human ToxChip comprising 2089 human clones, which were selected

> ... for their well-documented involvement in basic cellular processes as well as their responses to different types of toxic insult. Included on this list are DNA replication and repair genes, **apoptosis genes**, and genes responsive to PAHs and dioxin-like compounds, peroxisome proliferators, estrogenic compounds, and oxidant stress. Some of the other categories of genes include transcription factors, oncogenes, tumor suppressor genes, cyclins, kinases, phosphatases, cell adhesion and motility genes, and homeobox genes. Also included in this group are 84 housekeeping genes, whose hybridization intensity is averaged and used for signal normalization of the other genes on the chip. [emphasis added]

*See also* Table 1 of Nuwaysir et al. (specifically listing genes involved in apoptosis as of special interest in making a human toxicology microarray).

The more genes that are available for use in toxicology testing, the more powerful the technique.

"Arrays are at their most powerful when they contain the entire genome of the species they are being used to study." John C. Rockett and David J. Dix, Application of DNA Arrays to Toxicology, Environ. Health Perspec. 107(8):681 (1999). Control genes are carefully selected for their stability across a large set of array experiments in order to best study the effect of toxicological compounds. See attached email from the primary investigator, Dr. Cynthia Afshari to an Incyte employee, dated July 3, 2000, as well as the original message to which she was responding. Thus, there is no expressed gene which is irrelevant to screening for toxicological effects, and all expressed genes have a utility for toxicological screening. This is true for both polynucleotides and polypeptides encoded by them.

Knowledge of the function of the polypeptide that a polynucleotide encodes is not necessary for the use of the polynucleotide in expression profiling or toxicology testing. Moreover, knowledge of the function of naturally occurring variants of a known polypeptide is not necessary for the use of the corresponding polynucleotides in expression profiling or toxicology testing. The use of a polynucleotide that encodes a variant of a HAPOP polypeptide (e.g., with at least 90% homology, as disclosed in the specification of the instant application), whether these sequences encode active or inactive polypeptides, is useful in expression profiling and in diagnosing diseases associated with apoptosis. The expression of such variants may be associated with (i) alternative splicing, (ii) the use of internal promoter elements, (iii) RNA editing, (iv) chromosomal deletion or translocation, (v) spontaneous or environmentally induced mutations, or other events that alter gene expression. The use of polynucleotide variants is particularly useful in identifying genetic polymorphisms (including but not limited to single nucleotide polymorphisms (SNP, SNiPs)) that are useful genotypic markers for genetic abnormalities. Furthermore, it would be obvious for one skilled in the art to made and test such variant polynucleotides for use in expression profiling and toxicology testing.

Similarly, it would be obvious to a practitioner skilled in the relevant art to use variant HAPOP polypeptides (e.g., variants of at least 90% identity to HAPOP) or fragments of HAPOP, based on the disclosed polypeptide and polynucleotide sequences of the instant application, for proteome expression profiling. Even in the absence of specific knowledge with respect to the function of these polypeptides, these variants and fragments are useful for expression profiling and toxicology testing with respect to polypeptides involved in apoptosis.

There are numerous uses for the information made possible by expression profiling (some of which are mentioned above). Expression profiling is used to identify drug targets and characterize disease. See Rockett et al., *supra*. It also is used in tissue profiling, developmental biology, disease staging, etc. There is simply no doubt that the sequences of expressed human genes all have practical, substantial and credible real-world utilities, at the very least for expression profiling.

Expression profiling technology is also used to identify drug targets and analyze disease at the molecular level, thus accelerating the drug development process. For example, expression profiling is useful for the elucidation of biochemical pathways, each pathway comprising a multitude of component polypeptides and thus providing a pool of potential drug targets. In this manner, expression profiling leads to the optimization of drug target identification and a comprehensive understanding of disease etiology and progression. There is simply no doubt that the sequences of expressed human polynucleotides and polypeptides all have practical, substantial and credible real-world utilities, at the very least for biochemical pathway elucidation, drug target identification, and assessment of toxicity and treatment efficacy in the drug development process. Sandra Steiner and N. Leigh Anderson, *supra*, have elaborated on this topic as follows:

> The rapid progress in genomics and proteomics technologies creates a unique opportunity to dramatically improve the predictive power of safety assessment and to accelerate the drug development process. Application of gene and protein expression profiling promises to improve lead selection, resulting in the development of drug candidates with higher efficacy and lower toxicity. The identification of biologically relevant surrogate markers correlated with treatment efficacy and safety bears a great potential to optimize the monitoring of pre-clinical and clinical trials.

In fact, the potential benefit to the public, in terms of lives saved and reduced health care costs, are enormous. Recent developments provide evidence that the benefits of this information are already beginning to manifest themselves. Examples include the following:

- In 1999, CV Therapeutics, an Incyte collaborator, was able to use Incyte gene expression technology, information about the structure of a known transporter gene, and chromosomal mapping location, to identify the key gene associated with Tangier disease. This discovery took place over a matter of only a few weeks, due to the power of these new genomics technologies. The discovery received an award from the American Heart Association as one of the top 10 discoveries associated with heart disease research in 1999.

- In an April 9, 2000, article published by the Bloomberg news service, an Incyte customer stated that it had reduced the time associated with target discovery and validation from 36 months to 18 months, through use of Incyte's genomic information database. Other Incyte customers have privately reported similar experiences. The implications of this significant saving of time and expense for the number of drugs that may be developed and their cost are obvious.

- In a February 10, 2000, article in the *Wall Street Journal*, one Incyte customer stated that over 50 percent of the drug targets in its current pipeline were derived from the Incyte database. Other Incyte customers have privately reported similar experiences. By doubling the number of targets available to pharmaceutical researchers, Incyte genomic information has demonstrably accelerated the development of new drugs.

Because the Patent Examiner failed to address or consider the "well-established" utilities for the

claimed invention in toxicology testing, drug development, and the diagnosis of disease, the Examiner's rejections should be overturned regardless of their merit.

**B. The use of HAPOP polypeptides for toxicology testing, drug discovery, and disease diagnosis are practical uses that confer "specific benefits" to the public**

Even if, *arguendo*, toxicology testing, drug development and disease diagnosis (through expression profiling) are not well-established utilities (which expressly is not conceded), the claimed invention nonetheless has specific utility by virtue of its use in each of these techniques. There is no dispute that the claimed invention is in fact a useful tool in each of these techniques. That is sufficient to establish utility for both the polypeptide and the polynucleotides encoding it.

Nevertheless, the claimed invention is rejected on the grounds that it does not have a "specific utility" absent a detailed description of the actual function of the protein expressed by the claimed nucleic acid or identification of a "specific" disease it can be used to treat. Apparently relying on the Training Materials, the rejection is made based on a scientifically incorrect and legally unsupportable assertion that identification of the family or families of proteins to which the claimed invention belongs, without more, does not satisfy the utility requirement. None of these grounds is consistent with the law.

**1. A patent applicant can specify a utility without any knowledge as to how or why the invention has that utility**

It is settled law that how or why any invention works is irrelevant to determining utility under 35 U.S.C. § 101: "[I]t is not a requirement of patentability that an inventor correctly set forth, or even know, how or why the invention works." *In re Cortright*, 165 F.3d, at 1359 (quoting *Newman v. Quigg*, 877 F.2d 1575, 1581, 11 USPQ2d 1340 (Fed. Cir. 1989)). *See also Fromson v. Advance Offset Plate, Inc.*, 720 F.2d 1565, 1570, 219 USPQ 1137 (Fed. Cir. 1983) ("[I]t is axiomatic that an inventor need not comprehend the scientific principles on which the practical effectiveness of his invention rests."). It follows that the patent applicant need not set forth the particular functionality of the claimed invention to satisfy the utility requirement.

Practical, beneficial use, not functionality, is at the core of the utility requirement. *Supra* (introduction to § I). So long as the practical benefits are apparent from the invention without speculation, the requirement is satisfied. *Standard Oil* Co. v. *Montedison*, 664 F.2d 356, 374, 212 USPQ 327 (3d Cir. 1981); *see also Brana*, 51 F.3d at 1565. To state that a biological molecule might be useful to treat some unspecified disease is not, therefore a specific utility. *In re Kirk*, 376 F.2d 936, 945, 153 USPQ 48 (C.C.P.A. 1967). The molecule might be effective, and it might not.

However, unlike the synthetic molecules of *Kirk*, the claimed invention is **known** to be useful. It is not just a random sequence of speculative use. Because it is expressed in **humans**, a person of

ordinary skill in the art would know how to use the claimed polynucleotide and/or polypeptide sequences -- without any guesswork -- in toxicology testing, drug development, and disease diagnosis regardless of how the polynucleotide or the protein it encodes actually functions. The claimed invention could be used, for example, in a toxicology test to determine whether a drug or toxin causes any change in the expression of proteins involved in apoptosis. Similarly, the claimed invention could be used to determine whether a specific medical condition, such as cancer, affects the expression of (or results from the altered expression of) proteins involved in apoptosis and, perhaps in conjunction with other information, serve as a marker for or to assess the stage of a particular disease or condition.

In fact, the claimed polypeptide and/or polynucleotide sequences could be used in toxicology testing and diagnosis without **any** knowledge (although this is not the case here) of the protein for which it codes: it could serve, for example, as a marker of a toxic response, or, alternatively, if levels of the claimed polypeptide or polynucleotide remain unchanged during a toxic response, as a control in toxicology testing. Diagnosis of disease (or fingerprinting using expression profiles) can be achieved using arrays of numerous identifiable, expressed DNA sequences, or by two-dimensional gel analysis of the expressed proteins themselves, notwithstanding lack of any knowledge of the specific functions of the proteins they encode.

**2. A patent applicant may specify a utility that applies to a broad class of inventions**

The fact that the claimed invention is a member of a broad class (such as DNA sequences or the proteins they encode expressed in humans) that includes sequences other than those claimed that also have utilities in toxicology testing, drug discovery, disease diagnosis, etc. does not negate utility. Practical utilities can be directed to classes of inventions, irrespective of function, so long as a person of ordinary skill in the art would understand how to achieve a practical benefit from knowledge of the class. *Montedison*, 664 F.2d at 374-75. The law has long assumed that inventions that achieve a practical use also achieved by other inventions satisfy the utility requirement. For example, many materials conduct electricity. Likewise, many different plastics can be used to form useful films. *Montedison*, 664 F.2d at 374-75; *Natta*, 480 F.2d at 1397. This is a general utility (practical films) that applies to a broad class of inventions (plastics) which satisfies the utility requirement of 35 U.S.C. § 101.

Not all broad classes of inventions are, by themselves, sufficient to inform a person of ordinary skill in the art of the practical utility for a member of the class. Some classes may indeed convey too little information to a person of ordinary skill in the art. These may include classes of inventions that include both useful and nonuseful members. *See In re Ziegler*, 992 F.2d 1197, 1201, 26 USPQ2d 1600 (Fed. Cir. 1993). In some of these cases, further experimentation would be required to determine whether or not a member of the class actually has a practical use. *Brenner*, 383 U.S. at 534-35.

The broad class of steroids identified in *Kirk* is just such a class. It includes natural steroids (concededly useful) and man-made steroids, some of which are useful and some of which are not. Indeed, only a small fraction of the members of this broad class of invention may be useful. Without additional information or further experimentation, a person of ordinary skill in the art would not know whether a member of the class falls into the useful category or not. This could also be the case for the broad class of "plastic-like" polypropylenes in *Ziegler*, which includes many -- perhaps predominately -- useless members.

The PTO routinely issues patents whose utility is based solely on the claimed inventions' membership in a class of useful things. The PTO presumably would issue a patent on a novel and nonobvious fishing rod notwithstanding the lack of any disclosure of the particular fish it might be used to catch. The standard being promulgated in the Guidelines and in particular as exemplified in the Training Materials, and being applied in the present rejection, would appear to warrant a rejection, however, on the grounds that the use of the fishing rod is applicable to the general class of devices used to catch fish.

The PTO must apply the same standard to the biotechnological arts that it applies to fields such as plastics and fishing equipment. *In re Gazave*, 379 F.2d 973, 977-78, 154 USPQ 92 (CCPA 1967) *quoting In re Chilowsky*, 299 F.2d 457, 461, 108 USPQ 321 (CCPA 1956) ("[T]he same principles should apply in determining operativeness and sufficiency of disclosure in applications relating to nuclear fission art as in other cases."); *see also In re Alappat*, 33 F.3d 1526, 1566, 31 USPQ2d 1545 (Fed. Cir. 1994) (Archer, C.J., concurring in part and dissenting in part) ("Discoveries and inventions in the field of digital electronics are analyzed according to the aforementioned principles [concerning patentable subject matter] as any other subject matter."). Indeed, there are numerous classes of inventions in the biotechnological arts that satisfy the utility requirement.

Take, for example, the class of interleukins expressed in human cells of the immune system. Unlike the classes of steroids or plastic-like polypropylenes in *Kirk* and *Ziegler*, all of the members of this class have practical uses well beyond "throwaway" uses. All of them cause some physiological response (in cells of the immune system). All of the genes encoding them can be used for toxicology testing to generate information useful in activities such as drug development, even in cases where little is known as to how a particular interleukin works. No additional experimentation would be required, therefore, to determine whether an interleukin has a practical use. It is well-known to persons of ordinary skill in the art that there is no such thing as a useless interleukin.

Because all of the interleukins, as a class, convey practical benefit (much like the class of DNA ligases identified in the Training Materials), there is no need to provide additional information about

them. A person of ordinary skill in the art need not guess whether any given interleukin conveys a practical benefit or how that particular interleukin works.

Another example of a class that by itself conveys practical benefits is the G protein-coupled receptors ("GPCRs"). GPCRs are well-known as intracellular signaling mediators with diverse functions critical to complex organisms. They perform these functions by binding to and interacting with specific ligands. They are targets of many current drug treatments, including anti-depressants, anti-histamines, blood pressure regulators, and opiates.

Newly-identified GPCRs are used intensively in the real-world, even in cases where neither the specific ligand that binds to the GPCR or the precise biological function of the GPCR is known. Newly identified GPCRs are used, for example, as toxicity controls for drug candidates known to bind other GPCRs. Because a person of ordinary skill in the art would know how to use any GPCR to achieve a practical benefit, even without any detailed or particular knowledge as to how it works, GPCRs as a class meet the utility requirement.

In fact, <u>**all**</u> isolated and purified naturally-occurring polynucleotide and polypeptide sequences which are expressable (i.e., which are not pseudogenes that are never expressed during any natural biological process) can be and **are** used in a real-world context as tools for toxicological testing, e.g., for drug discovery purposes. This utility applies to all sequences actually expressed, yet in each case, the utility of the sequence is quite specific, e.g., insofar as it is used to detect its own specific complementary sequence in a sample containing many different sequences.

Proteins involved in apoptosis, like interleukins, GPCRs and fishing rods is a class that by itself conveys practical benefits. Unlike steroids and "plastic-like" polypropylenes, all of the proteins involved in apoptosis are expressed by humans, and all of them can be used as tools for toxicology testing. The claimed invention could be used, for example to determine whether a drug candidate induces apoptosis, how it does so, and to what extent. Just as there are no useless interleukins and GPCRs, there are no useless proteins involved in apoptosis. As these are practical, real-world uses, the application need not describe particular functionality or medical applications that would only supplement the utilities known to exist already.

**C. Because the use of proteins involved in apoptosis in toxicology testing, drug discovery, and disease diagnosis are practical uses beyond mere study of the invention itself, the claimed invention has substantial utility.**

In addition to conferring a specific benefit on the public, the benefit must also be "substantial." *Brenner*, 383 U.S. at 534. A "substantial" utility is a practical, "real-world" utility. *Nelson v. Bowler*,

626 F.2d 853, 856, 206 USPQ 881 (CCPA 1980).

The claimed invention's use as a tool for toxicology testing is just such a practical, real-world use. The PTO nonetheless rejected the claims at issue on the ground that the use of an invention as tool for research is not a "substantial" use. Because the PTO's rejection assumes a substantial overstatement of the law, it must be overturned.

There is no authority for the proposition that use as a tool for research is not a substantial utility. In fact, the PTO issues patents for inventions whose only use is to facilitate research, such as DNA ligases. These are acknowledged by the PTO's Training Materials themselves to be useful.

Only a limited subset of research uses are not "substantial" utilities: those in which the only known use for the claimed invention is to be an **object** of further study, thus merely inviting further research. This follows from *Brenner*, in which the U.S. Supreme Court held that a process for making a compound does not confer a substantial benefit where the only known use of the compound was to be the object of further research to determine its use. *Id.* at 535. Similarly, in *Kirk*, the held that a compound would not confer substantial benefit on the public merely because it might be used to synthesize some other, unknown compound that would confer substantial benefit. *Kirk*, 376 F.2d at 940, 945 ("What appellants are really saying to those in the art is take these steroids, experiment, and find what use they do have as medicines."). Nowhere do those cases state or imply, however, that a material cannot be patentable if it has some other beneficial use in research.

As used in toxicology testing, drug discovery, and disease diagnosis, the claimed invention has a beneficial use in research other than studying the claimed invention or its protein products. It is a tool, rather than an object, of research. The claimed invention has numerous other uses as a research tool, each of which alone is a "substantial utility". These include: **use in toxicology testing to determine the effect of exogenous drugs and xenobiotic compounds on HAPOP activity, use a targets for the development of inhibitory molecules to inhibit or induce apoptosis, use in isolating HAPOP target molecules from human cell lysates, use in raising antibodies for use in diagnosing overexpression, ectopic expression, or lack of expression of these polypeptides in individuals, and use at a suicide gene for transformed cells.**

**D. Objective evidence corroborates the utilities of the claimed invention**

There is in fact no restriction on the kinds of evidence a Patent Examiner may consider in determining whether a "real-world" utility exists. Indeed, "real-world" evidence, such as evidence showing actual use or commercial success of the invention, can demonstrate conclusive proof of utility. *Raytheon v. Roper*, 220 USPQ2d 592 (Fed. Cir. 1983); *Nestle v. Eugene*, 55 F.2d 854, 856, 12 USPQ 335

(6th Cir. 1932). Indeed, proof that the invention is made, used or sold by any person or entity other than the patentee is conclusive proof of utility. *United States Steel Corp.* v. *Phillips Petroleum Co.*, 865 F.2d 1247, 1252, 9 USPQ2d 1461 (Fed. Cir. 1989).

Over the past several years, a vibrant market has developed for databases containing all expressed genes (along with the polypeptide translations of those genes), in particular genes having medical and pharmaceutical significance such as the instant sequence. (Note that the value in these databases is enhanced by their completeness, but each sequence in them is independently valuable.) The databases sold by Appellants' assignee, Incyte, include exactly the kinds of information made possible by the claimed invention, such as tissue and disease associations. Incyte sells its database containing the claimed sequence and millions of other sequences throughout the scientific community, including to pharmaceutical companies who use the information to develop new pharmaceuticals.

## II. The Patent Examiner Failed to Demonstrate That a Person of Ordinary Skill in the Art Would Reasonably Doubt the Utility of the Claimed Invention

In addition to alleging a "specific" use for the claimed subject matter, a patent applicant must present proof that the claimed subject matter is in fact useful. *Brana*, 51 F.3d at 1565-66. The applicant need only prove a "substantial likelihood" of utility; certainty is not required. *Brenner*, 383 U.S. at 532.

The amount of evidence required to prove utility depends on the facts of each particular case. *In re Jolles*, 628 F.2d 1322, 1326, 206 USPQ 885 (CCPA 1980). "The character and amount of evidence may vary, depending on whether the alleged utility appears to accord with or to contravene established scientific principles and beliefs." *Id.* Unless there is proof of "total incapacity," or there is a "complete absence of data" to support the applicant's assertion of utility, the utility requirement is met. *Brooktree Corp. v. Advanced Micro Devices, Inc.*, 977 F.2d 1555, 1571, 24 USPQ2d 1401 (Fed. Cir. 1992); *Envirotech*, 730 F.2d at 762.

A patent applicant's assertion of utility in the disclosure is presumed to be true and correct. *In re Cortright*, 165 F.3d at 1356; *Brana*, 51 F.3d at 1566. If such an assertion is made, the Patent Office bears the burden in the first instance to demonstrate that a person of ordinary skill in the art would reasonably doubt that the asserted utility could be achieved. *Ids.* To do so, the PTO must provide evidence or sound scientific reasoning. *See Langer*, 503 F.2d at 1391-92. If and only if the Patent Office makes such a showing, the burden shifts to the applicant to provide rebuttal evidence that would convince the person of ordinary skill that there is sufficient proof of utility. *Brana*, 51 F.3d at 1566. The Revised Guidelines are in agreement with this procedure. *See* Revised Interim Guidelines at ¶¶ 3-4.

The issue of proof often arises in the chemical and biotechnological arts when the patentee

asserts a utility for a claimed chemical compound based on its homology or similarity to another compound having a known, established utility. In such cases, the applicant can demonstrate "substantial likelihood" of utility by demonstrating a "reasonable correlation" between the utility -- not the function -- of the known compound and the compound being claimed. *Fujikawa v. Wattanasin*, 93 F.3d 1559, 1565, 39 USPQ2d 1895 (Fed. Cir. 1996). Accordingly, under *Brana*, the Patent Office must accept the asserted utility unless it can show that a person of ordinary skill in the art would reasonably doubt that a "reasonable correlation" exists. If the Patent Office makes such a showing, however, the applicant may submit evidence in support of the correlation.

In the present case, the Examiner has assumed that a practitioner skilled in the relevant art would not know how to use polypeptides involved in apoptosis, fragments of these polypeptides, or variants of these polypeptides. The only evidence of record shows that a person of ordinary skill in the art would not doubt that proteins involved in apoptosis is in fact a **specific genus of cellular proteins**, which is known to have a specific utility.

By ignoring the "reasonable correlation" requirement in the case law and failing to illustrate the procedure established by *Brana*, the Examiner has failed to set forth a proper *prima facie* case, and the rejection does not shift the burden of proof to Appellants for rebuttal. In fact, the rejection must be withdrawn, as the Examiner has failed to meet PTO's burden in the first place of establishing a proper rejection. There is no proper rejection for Appellants to rebut.

## III. By Requiring the Patent Applicant to Assert a Particular or Unique Utility, the Patent Examination Utility Guidelines and Training Materials Applied by the Patent Examiner Misstate the Law

The Training Materials, which direct the Examiners regarding how to apply the Utility Guidelines, address the issue of specificity with reference to two kinds of asserted utilities: "specific" utilities which meet the statutory requirements, and "general" utilities which do not. The Training Materials define a "specific utility" as follows:

> A [specific utility] is *specific* to the subject matter claimed. This contrasts to *general* utility that would be applicable to the broad class of invention. For example, a claim to a polynucleotide whose use is disclosed simply as "gene probe" or "chromosome marker" would not be considered to be specific in the absence of a disclosure of a specific DNA target. Similarly, a general statement of diagnostic utility, such as diagnosing an unspecified disease, would ordinarily be insufficient absent a disclosure of what condition can be diagnosed.

The Training Materials distinguish between "specific" and "general" utilities by assessing whether the asserted utility is sufficiently "particular," *i.e.*, unique (Training Materials at p.52) as compared to the "broad class of invention." (In this regard, the Training Materials appear to parallel the

view set forth in Stephen G. Kunin, Written Description Guidelines and Utility Guidelines, 82 J.P.T.O.S. 77, 97 (Feb. 2000)("With regard to the issue of specific utility the question to ask is whether or not a utility set forth in the specification is *particular* to the claimed invention.")).

Such "unique" or "particular" utilities never have been required by the law. To meet the utility requirement, the invention need only be "practically useful," *Natta*, 480 F.2d 1 at 1397, and confer a "specific benefit" on the public. *Brenner*, 383 U.S. at 534. Thus incredible, "throwaway" utilities, such as trying to "patent a transgenic mouse by saying it makes great snake food" do not meet this standard. Karen Hall, Genomic Warfare, The American Lawyer 68 (June 2000) (quoting John Doll, Chief of the Biotech Section of USPTO).

This does not preclude, however, a general utility, contrary to the statement in the Training Materials where "specific utility" is defined (page 5). Practical real-world uses are not limited to uses that are unique to an invention. The law requires that the practical utility be "definite," not particular. *Montedison,* 664 F.2d at 375. Appellant is not aware of any court that has rejected an assertion of utility on the grounds that it is not "particular" or "unique" to the specific invention. Where courts have found utility to be too "general," it has been in those cases in which the asserted utility in the patent disclosure was not a practical use that conferred a specific benefit. That is, a person of ordinary skill in the art would have been left to guess as to how to benefit at all from the invention. In *Kirk*, for example, the CCPA held the assertion that a man-made steroid had "useful biological activity" was insufficient where there was no information in the specification as to how that biological activity could be practically used. *Kirk*, 376 F.2d at 941.

The fact that an invention can have a particular use does not provide a basis for requiring a particular use. *See Brana*, *supra* (disclosure describing a claimed antitumor compound as being homologous to an antitumor compound having activity against a "particular" type of cancer was determined to satisfy the specificity requirement). "Particularity" is not and never has been the *sine qua non* of utility; it is, at most, one of many factors to be considered.

As described *supra*, broad classes of inventions can satisfy the utility requirement so long as a person of ordinary skill in the art would understand how to achieve a practical benefit from knowledge of the class. Only classes that encompass a significant portion of nonuseful members would fail to meet the utility requirement. *Supra* § II.B.2 (*Montedison,* 664 F.2d at 374-75).

The Training Materials fail to distinguish between broad classes that convey information of practical utility and those that do not, lumping all of them into the latter, unpatentable category of "general" utilities. As a result, the Training Materials paint with too broad a brush. Rigorously applied, they would render unpatentable whole categories of inventions heretofore considered to be patentable,

and that have indisputably benefitted the public, including the claimed invention. *See supra* § II.B. Thus the Training Materials cannot be applied consistently with the law.

**IV. To the extent the rejection of the patented invention under 35 U.S.C. § 112, first paragraph, is based on the improper rejection for lack of utility under 35 U.S.C. § 101, it must be reversed.**

The rejection set forth in the Office Action is based on the assertions discussed above, i.e., that the claimed invention lacks patentable utility. To the extent that the rejection under § 112, first paragraph, is based on the improper allegation of lack of patentable utility under § 101, it fails for the same reasons.

**Rejections under 35 U.S.C. §§ 102(b) and 102(e)**

Claims 21 and 27 stand rejected under 35 U.S.C. § 102(e) as being anticipated by U.S. Patent Nos.: 5,925,733 and 5,919,660 (paragraphs 16-17 or the Office Action). In neither case is the homologous fragment cited by the Examiner longer than 6 amino acid residues. While such a fragment may be immunogenic (and any objection to claims 21 and/or 27 on this basis are obviated by the amendment to claim 21, herein), Applicants strenuously object to the scientifically incorrect and unsupported assertion that such a fragment be considered biologically active by one skilled in the art.

Claim 21 also stands rejected under 35 U.S.C. § 102(b) as being anticipated by Gabig et al. (1994). In this case, the homologous fragment cited by the Examiner is 7 contiguous amino acids. Again, while such a fragment may be immunogenic (and any objection to claims 21 and/or 27 on this basis are obviated by the amendment to claim 21, herein), such a fragment would certainly **not** be considered biologically active by one skilled in the art.

Claims 21 also stands rejected under 35 U.S.C. § 102(b) as being anticipated by Accession No.: A42445. In this case, the homologous fragment cited by the Examiner is 29 contiguous amino acids. The amendment to claim 21, herein, distinguishes the claimed invention of the instant application from A42445. Such a fragment is also unlikely to be biologically active. Nonetheless, assuming such a fragment retained the activity of the polypeptide from which it was derived, such a fragment would function to promote the differentiation of adipocytes by upregulating the transcription of fat-specific gene, FSP27 (Danesch, U. et al. (1992) J. Biol. Chem. 267:7185-7193; abstract enclosed). This biological activity is distinct from that of the polypeptides of claim 21 (i.e., to function in apoptosis). While HAPOP-2 shares limited structural similarities with FSP27, the expression of HAPOP-2 is associated with proliferative and cancerous tissues as opposed to differentiating adipose tissues. The objection to claim 21 on this basis is obviated by the amendments to claim 21, herein.

## CONCLUSION

Appellants respectfully submit that rejections for lack of utility based, *inter alia*, on an allegation of "lack of specificity" as set forth in the Office Action and as justified in the Revised Interim Utility Guidelines and Training Materials, are not supported in the law. Neither are they scientifically correct, nor supported by any evidence or sound scientific reasoning. These rejections are alleged to be founded on facts in court cases such as *Brenner* and *Kirk*, yet those facts are clearly distinguishable from the facts of the instant application, and indeed most if not all nucleotide and protein sequence applications. Nevertheless, the PTO is attempting to mold the facts and holdings of these prior cases, to target rejections of claims to polypeptide and polynucleotide sequences where biological activity information has not been proven by laboratory experimentation, and they have done so by ignoring perfectly acceptable utilities fully disclosed in the specifications as well as well-established utilities known to those of skill in the art. As is disclosed in the specification, and even more clearly, as one of ordinary skill in the art would understand, the claimed invention has well-established, specific, substantial and credible utilities. The rejections are, therefore, improper and should be reversed.

In light of the above amendments and remarks, Applicants submit that the present application is fully in condition for allowance, and request that the Examiner withdraw the outstanding rejections. Early notice to that effect is earnestly solicited.

Applicants believe that no fee is due with this communication. However, if the USPTO determines that a fee is due, the Commissioner is hereby authorized to charge Deposit Account No. **09-0108. This form is enclosed in duplicate.**

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Respectfully submitted,
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